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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,235	02/20/2001	Hicham Moulay Alaoui Ismaili	PHARMA-115	4355

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EXAMINER
LEWIS, PATRICK T

ART UNIT	PAPER NUMBER
1623	10

DATE MAILED: 12/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/785,235	ISMAILI ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of species A1 (method for treating Hepatitis C) and species B2 (wherein group B is a pyrimidine or an analogue thereof) in Paper No. 9 dated October 23, 2002 is acknowledged.

Claim Objections

2. Claim 1 is objected to because of the following informalities: In line 3, the examiner suggests incorporating language indicating to whom the therapeutic composition is administered. The examiner suggests adding the phrase "to a host in need thereof," after the term "effective amount". In line 16 the term "are" should be replaced with the term "is". Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the term "analogue" renders the instant claim and all subsequent depending claims in which the variable **B** is not clearly defined indefinite. Applicant has

failed to particularly point out the modifications to the pyrimidine moiety which distinctly set forth the structural core modifications or chemical moieties effectuating derivatization. In the absence of distinct modifications or derivatizing moieties, the term "analogue" is indefinite in all occurrences.

In claim 1, the alternative manner in which applicant defines variables represented by **Ra** renders the instant claim and all subsequent depending claims in which the variable **Ra** has not been clearly defined indefinite. It is unclear whether the terms appearing after the phrase "carbonyl substituted with a C_{1-6} alkyl" are intended to represent moieties attached to the carbonyl or if said terms represent moieties attached directly to the oxygen atom.

In claim 1, variables $\mathbf{D_1}$ and $\mathbf{D_2}$ have not been clearly defined. The phrase "can also be" renders the instant claim and all subsequent depending claims in which variables $\mathbf{D_1}$ and $\mathbf{D_2}$ have not been clearly defined indefinite. The phrase "can also be joined" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "can also be joined"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

5. In claims 12 and 13, the parenthetical phrase "(ribarivin base)" renders the claim indefinite because it is unclear whether the limitation(s) enclosed in parentheses are part of the claimed invention. See MPEP § 2173.05(d).

6. Claim 14 recites the limitation "according to claim 1 wherein the compound of formula I is chosen" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1, 2, 4, 6, 10, 12, and 15-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Tan et al. WO 00/50064 (Tan).

Tan discloses a method for treating flavivirus or rhabdovirus infection comprising administering to the host an interferon and nucleoside of formula (I) wherein –**X**- is =CH-, -CH2-, or –O-; **Nu** is selected from the group consisting of purines, pyrimidines, and five- or six-member aglycones; $\mathbf{R_2}$ and $\mathbf{R_3}$ are independently selected from the group consisting of H, OH, O-acyl, O-aryl, and O-silyl; and $\mathbf{R_1}$ is as defined for $\mathbf{R_2}$ and $\mathbf{R_3}$ or is O-phosphate (Page 2, lines 6-25). Specific compounds disclosed by Tan, which read on the instantly claimed method of the treatment include 3-deazauridine and 6-azauridine (Page 14, Table 1). The flavivirus maybe yellow fever virus, kunjin virus, dengue virus, hepatitis C virus, or an encephalitis virus (page 17, lines 16-20). The interferon may be an interferon α, such as interferon α2 or α8, or interferon β (Page 5, lines 27-30). Thus, the instantly claimed invention was anticipated by Tan et al.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Tan et al. WO 00/50064 (Tan), Johansson et al. U.S. Patent 5,506,215 (Johansson), and Hamedi-Sangsari et al. U.S. Patent 5,705,522 (Hamedi).

Claims 1-18 are drawn method of treating a hepatitis C infection in a host comprising administering a therapeutically effective amount of a compound of formula (Ib) or a pharmaceutically acceptable salt thereof. Claims 2 and 14-15 depend from claim 1. Claim 2 limits **Z** to OH. Claim 14 limits formula (I) to one of Compounds 1-54. Claim 15 is drawn to a method wherein said compound is used in combination with at least one further therapeutic agent. Claims 3-6, 10, 12, and 16 depend from claim 2. Claim 3 limits $\mathbf{D_1}$ to H and $\mathbf{D_2}$ to F. Claims 4-6 limit **Ra** to H, monophosphate, diphosphate, and triphosphate; triphosphate; and H, respectively. Claims 10 and 12 limit **B**. Claim 16 is drawn to a method wherein said compound is used in combination with at least one further therapeutic agent. Claims 7-9, 11, 13, and 17 depend from claim 3. Claims 7-9 limit **Ra** to H, monophosphate, diphosphate, and triphosphate; triphosphate; and H, respectively. Claims 11 and 13 limits **B**. Claim 17 is drawn to a method wherein said compound is used in combination with at least one further therapeutic agent.

Tan teaches a method for treating flavivirus or rhabdovirus infection comprising administering to the host an interferon and nucleoside of formula (I) wherein –**X**- is =CH- , -CH2-, or –O-; **Nu** is selected from the group consisting of purines, pyrimidines, and five- or six-member aglycones; $\mathbf{R_2}$ and $\mathbf{R_3}$ are independently selected from the group consisting of H, OH, O-acyl, O-aryl, and O-silyl; and $\mathbf{R_1}$ is as defined for $\mathbf{R_2}$ and $\mathbf{R_3}$ or is O-phosphate (Page 2, lines 6-25). Specific compounds taught by Tan, which overlap with the instantly claimed compounds of the treatment method include 3-deazauridine and 6-azauridine (Page 14, Table 1). The flavivirus maybe yellow fever virus, kunjin

virus, dengue virus, hepatitis C virus, or an encephalitis virus (page 17, lines 16-20). The interferon may be an interferon α, such as interferon α2 or α8, or interferon β (Page 5, lines 27-30).

Tan differs from the instantly claimed invention in that Tan: 1) does not teach $\mathbf{R_2}$ [$\mathbf{D_2}$] as being F; 2) does not teach explicitly teach $\mathbf{R_1}$ as being triphosphate but rather teaches O-phosphates in general; and 3) does not teach the specific embodiments of formula (I) described in claim 14. These deficiencies, however, would have been obvious to the skilled artisan in view of the teachings of Johansson and Hamedi.

Johansson teaches analogous pyrimidine nucleosides of formula (I) useful for the treatment of infections caused by retroviruses and hepatitis B virus in mammals and man wherein $\mathbf{R^6}$ [$\mathbf{D_2}$] is F (column 4, lines 50-55; column 3, line 45 through column 4, line 49). Johansson further teaches the compounds of formula (I) cooperate synergistically or additively with a wide range of other therapeutic agents, thereby enhancing the therapeutic potential of both agents with adding the toxic effects, thus increasing the therapeutic ratio (column 8, lines 42-46).

Hamedi teaches the use of analogous nucleosides (AZT, ddC, ddA, ddG, ddI, ddT, 3TC, and d4T) useful for treating both hepatitis B and hepatitis C viruses (column 3, lines 22-54).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Tan, Johansson, and Hamedi in order to treat patients suffering from hepatitis C with the instantly disclosed nucleoside derivatives. A *prima facie* case of obviousness may be made when chemical compounds have very

close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979).

Conclusion

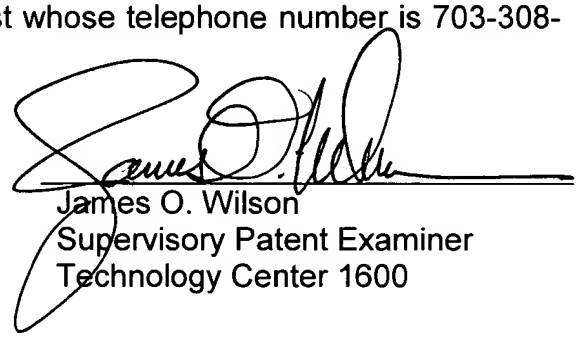
13. Claims 1-18 are pending. Claims 1-18 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 10:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



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ptl
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